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# Effect of fetal gender on maternal asthma exacerbations in pregnant asthmatic women

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**Summary**
Recent studies have found that asthmatic women pregnant with a female fetus reported more symptoms and had slightly lower lung function than women pregnant with a male fetus. In order to further investigate this association, we studied the effect of fetal sex on maternal asthma exacerbations and the use of asthma medications during pregnancy. A large cohort of pregnant asthmatic women and their babies was reconstructed between 1990 and 2002 from the linkage of three administrative databases of the Canadian province of Quebec. Asthma exacerbations were defined as a filled prescription of oral corticosteroids, an emergency department visit, or a hospitalization for asthma. Women pregnant with a female fetus were compared to women with a male fetus with respect to their rate of asthma exacerbation, their weekly doses of inhaled short-acting beta$_2$-agonists (SABA), and their daily dose of inhaled corticosteroids (ICS) during pregnancy. Logistic and linear regression models were used to obtain effect measures adjusted for several potential confounders such as asthma severity and control prior to pregnancy. The cohort included 5529 pregnancies with a single female fetus and 5728 pregnancies with a single male fetus. No significant differences were found between mothers of a female and male fetus as to the occurrence of asthma exacerbations (adjusted rate ratio = 1.02; 95% CI: 0.92–1.14), the daily dose of ICS (adjusted mean difference (AMD): 2.46 μg; 95% CI: −4.01 to 8.93), and the weekly dose of SABA (AMD: 0.004 dose; 95% CI: −0.23 to 0.24). Based on the results, we conclude that fetal gender is unlikely to affect maternal asthma during pregnancy to the point where acute care and medications are more often required among women pregnant with a female fetus.


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## Introduction

The prevalence of asthma among pregnant women varies between 4 and 7% and it is known as one of the most frequent chronic diseases encountered during pregnancy.[1–5] The course of asthma may remain unchanged, improve or worsen during pregnancy and usually returns to the pre-pregnancy state within three months after delivery.[6,7] The control of asthma during pregnancy can be influenced by several factors, namely physiologic hormonal changes that are triggered during pregnancy.[7]

A few studies have suggested that a pregnant woman's asthma may worsen when carrying a female fetus.[8–11] In a review of case series,[11] three mothers who had been followed in successive pregnancies reported more asthma attacks when pregnant with a female fetus than when they were carrying a male fetus. Moreover and in comparison with mothers carrying a male fetus, Beecroft et al. observed that pregnant asthmatic mothers with a female fetus had reported an increase in asthma symptoms[8] while Dodds et al.[9] observed that they had an increased usage of steroids. More recently, Kwon et al. assessed the association between fetal gender and airway lability among pregnant asthmatic women and found a 10% significant reduction in peak expiratory flow rate (PEF) among mothers with a female fetus. Conversely, Baibergenova et al. did not find any significant association between fetal gender and visits to an emergency department (ED) for asthma during pregnancy.[12] Among the hypotheses put forward to explain the mechanisms behind the association between fetal gender and maternal asthma control during pregnancy, the one related to the regulation of placental glucocorticoid and immune response in asthmatic pregnancies seems the most plausible.[8,10,12] Indeed, Clifton and Murphy and their research teams have reported that female fetus alters maternal asthma during pregnancy by upregulating maternal inflammatory pathways[13–16] and thus if asthma-associated inflammatory pathways are not treated with inhaled steroids during pregnancy, the mother could suffer from asthma exacerbation.

Although studies have reported possible associations between fetal gender and maternal asthma control during pregnancy, methodological issues such as the measure of the outcome and the absence of statistical inference, as well as the questionable clinical significance of some of the results make it difficult to conclude with a reasonable degree of certainty that women pregnant with a female fetus are more likely to have uncontrolled asthma. Using Canadian administrative databases, we planned a large cohort study to further evaluate the effect of fetal gender on the risk of uncontrolled maternal asthma through the study of exacerbations, use of inhaled short-acting beta$_2$-agonists (SABA) and inhaled corticosteroids (ICS) during pregnancy.

## Materials and methods

### Source of data

The data for our study came from three administrative databases of the Canadian province of Québec; the *Régie de l'Assurance Maladie du Québec* (RAMQ), MED-ECHO, and the *Fichier des événements démographiques du Québec* (birth and death registries) managed by the *Institut de la statistique du Québec* (ISQ). RAMQ databases provide information on the medical services dispensed to all residents of Québec and on prescribed medications filled in community pharmacies by residents covered by the RAMQ's Public Drug Insurance Plan. Approximately 43% of the population of Quebec is covered by the RAMQ Public Drug Insurance Plan, most notably the elderly and social aid beneficiaries since 1980 and since 1997, 1.7 million new adherents, mainly workers and their families who have no access to a private drug insurance plan.[17] The RAMQ's Prescription Drug Insurance database provides information on dispensed medications — i.e. date of filling, name, dose, quantity, dosage form and duration of the prescription — while the RAMQ's Medical Services database provides information on medical services dispensed in a clinic, an emergency department (ED) or a hospital (date, diagnosis coded with ICD-9, where the service was dispensed, etc.). The RAMQ databases also provide socio-demographic data such as age, gender, social assistance status and where relevant, date of death. Data recorded in the RAMQ Prescription Drug Insurance database and asthma diagnoses recorded in the RAMQ Medical Services database have been formally evaluated and found to be valid.[18,19] The MED-ECHO database is a provincial database which records data on acute care hospitalizations and covers all residents of Quebec. For each hospitalization, data on primary and up to 15 secondary discharge diagnoses, date of entry, duration of hospitalization, and treatments received during the hospitalization are available.[19] The *Fichier des événements démographiques* provides information on all births and stillbirths in the province of Québec.

### Study design and population

A large cohort of pregnant asthmatic women and their babies was reconstructed between 1990 and 2002 from the linkage of the three administrative databases. Pregnant women were identified using diagnostic and act codes related to prenatal care, pregnancy complications, abortions and deliveries.[20] To be included in our cohort, a woman should have: (1) had one or more singleton pregnancies ending in a delivery (life birth or stillbirth) between January 1, 1990 and December 31, 2002; (2) been between 13 and 50 years of age at conception; (3) had in the two years prior to, or during pregnancy, a diagnosis of asthma (9th international classification of diseases (ICD-9) code 493, except 493.2 which relates to COPD disease) and one or more prescriptions for an asthma medication (ICS, oral corticosteroids, SABA, long-acting beta$_2$-agonists (LABA), theophyllines, leukotriene-receptor antagonists, inhaled short-acting anticholinergic, cromoglycate or nedocromil) dispensed; (4) had coverage with the RAMQ Drug Insurance Plan for at least one year prior to, and throughout the duration of pregnancy; and (5) had no other pregnancy of more than 14 weeks in the year prior to conception. The length of gestation was obtained mainly from the MED-ECHO database, which was calculated based upon the date of the last menstruation. To assess the date of conception, we subtracted the length of gestation from the date of the

delivery. The unit of analysis was pregnancy; a woman could contribute more than one pregnancy in the cohort.

For each included woman, data from RAMQ and MED-ECHO were obtained for the two years preceding conception, and the duration of the pregnancy. This mother—child cohort was then linked with the *Fichier des événements démographiques* databases to obtain information on socio-demographic variables for the mothers and the newborns.

### Fetal gender

The gender of the baby was extracted from the RAMQ database and was checked for consistency with that recorded in the ISQ and MED-ECHO databases. In case of missing values or inconsistencies, the following algorithm was used to determine the gender: (1) if the gender of the baby was recorded in the RAMQ database then this value was retained; (2) if the gender of the baby was missing at RAMQ and recorded at ISQ then the ISQ value was retained; and (3) if the gender of the baby was missing at RAMQ and ISQ, the value recorded at MED-ECHO was retained. If the gender of the baby was not recorded in any of the three databases, the pregnancy was excluded. Fetal gender has been formally evaluated and found to be highly valid as compared to the information recorded in the medical chart of the mother with specificity and sensitivity higher than 0.97.[21]

### Primary and secondary outcomes

The primary outcome was asthma exacerbations during pregnancy. Based upon the criteria used in the Canadian Asthma Consensus Guidelines, asthma exacerbations were defined as a short ($\leq$14 days) course of oral corticosteroids dispensed by a pharmacy, an ED visit for asthma, or a hospitalization for asthma.[22] To avoid the overestimation of the number of exacerbations, all the aforementioned events occurring within a 15-day period accounted for one exacerbation. Asthma diagnoses recorded in the RAMQ databases have been formally evaluated and found to be valid.[19]

The secondary outcomes included the mean daily dose of ICS and the mean weekly dose of SABA during pregnancy, calculated using data from the RAMQ's database using validated algorithms based upon the name, dose, formulation and quantity of the dispensed medication, duration of the prescription and time intervals between renewals.[20,23] The equivalencies of the mean daily dose of ICS into beclomethasone-CFC were calculated using the equivalency table published in the Canadian Asthma Consensus Guidelines.[22] The equivalencies for SABA were established by a pharmacist (MFB); for example, one dose of SABA was equivalent to two inhalations of salbutamol from a metered-dose inhaler (100 $\mu$g per inhalation).[23]

### Data analysis

Descriptive statistics were calculated by fetal gender for socio-demographic variables, antiasthmatic medication use, and health care services use for asthma during pregnancy. Crude rates of maternal asthma exacerbation during the whole pregnancy and for each trimester separately were compared between pregnancies of a female and male fetus.

Logistic regression models were used to obtain odds ratios of exacerbation adjusted for several potential confounders including socio-demographic variables such as maternal age at conception ($<$18, 18—34, $>$34 years), social assistance benefits one year before or during pregnancy (yes/no), area of residency at delivery (rural or urban); pregnancy related variables such as being primiparous (yes/no), high risk pregnancy (yes/no), gestational diabetes (yes/no), diabetes mellitus (yes/no), pregnancy induced hypertension (yes/no), chronic hypertension (yes/no), gynecologist or obstetrician visit during pregnancy (yes/no), number of prenatal visits ($\leq$5, 6—14, $>$14); as well as asthma related variables such as a respiratory specialist visit during pregnancy (yes/no), ICS use during pregnancy (yes/no), and asthma severity and control prior to pregnancy. Asthma severity and control were measured with validated database indexes that we developed based on medication use and the need for acute care for asthma.[24] We used a backward elimination strategy to find final logistic regression models including covariates that changed the odds ratio associated with the gender of the baby by at least 10% and covariates that were found to be statistically associated with the outcome. Adjusted effects of fetal gender were estimated for the whole pregnancy and for each trimester separately. The first, second and third trimesters of pregnancy were defined as periods between 0 and 14 weeks of pregnancy, between 15 and 28 weeks of pregnancy and from the 29th week up to the end of pregnancy, respectively.

Adjusted differences in the mean daily dose of ICS and mean weekly dose of SABA were estimated between all pregnancies of female and male fetuses using linear regression models and the aforementioned potential confounders. Adjusted differences were estimated for the whole pregnancy and for each trimester separately.

One secondary analysis was performed on the primary outcome. For this analysis, we selected the women who had at least two pregnancies during the study period with fetuses of different sex. For these women, the rate of asthma exacerbations during the whole pregnancy was compared between pregnancies of a female and male fetus using logistic regression models. All statistical analyses were performed using SAS version 8.02.

## Results

### Study population characteristics

Among the 13 040 pregnancies included in the cohort of asthmatic women, 1774 were excluded because there was another pregnancy of 14 weeks or more in the year prior to conception and nine pregnancies were excluded because the baby's gender was unknown. The final cohort included 11 257 singleton pregnancies with 5529 female (49.1%) and 5728 male (50.9%) fetuses. The rate of concordance for fetal gender between the three databases was 99%.

In Table 1, we present the socio-demographic and pregnancy related characteristics of the study women, by fetal gender. The female and male fetus groups showed comparable characteristics. In Table 2, we present the asthma related characteristics in the year before conception and

**Table 1** Socio-demographic and pregnancy related characteristics of study women by fetal gender.

| | Pregnancies of female fetus | Pregnancies of male fetus |
|---|---|---|
| Numbers | 5529 | 5728 |
| Age at conception (years), mean ± s.d | 25.0 ± 5.6 | 24.9 ± 5.6 |
| Social assistance,[a] % | 78.9 | 78.3 |
| Urban residency at delivery, % | 80.7 | 81.3 |
| Primiparous, % | 36.9 | 37.3 |
| High risk pregnancy, % | 35.6 | 36.3 |
| Gestational diabetes, % | 8.1 | 7.6 |
| Chronic diabetes, % | 2.3 | 2.7 |
| Pregnancy induced hypertension, % | 7.0 | 6.7 |
| Chronic hypertension, % | 2.6 | 2.3 |
| Gynecologist or obstetrician visit during pregnancy, % | 82.2 | 83.3 |
| Number of prenatal visits, % | | |
| ≤5 | 15.1 | 14.5 |
| 6–14 | 73.3 | 73.0 |
| >14 | 11.7 | 12.5 |
| Season of delivery, % | | |
| Winter | 24.4 | 23.9 |
| Spring | 26.2 | 27.2 |
| Fall | 24.0 | 23.9 |
| Summer | 25.4 | 25.0 |

[a] Recipient of social assistance in the year prior to or during pregnancy.

during pregnancy, by fetal gender. All characteristics were distributed similarly among female and male fetus pregnancies for these two periods.

## Maternal asthma exacerbation during pregnancy by fetal gender

In Table 3, we present the proportion of women who had at least one asthma exacerbation within each trimester separately and during the entire pregnancy, by fetal gender. During the first trimester, 6.9% and 6.8% of women carrying a female and male fetus had at least one asthma exacerbation, respectively. In the second trimester, this proportion remained unchanged for the female fetus group, but increased modestly to 7.1% for the male fetus group. During the third trimester, the rate of maternal asthma exacerbations decreased to 4.0% and 3.7% for mothers of female and male fetuses, respectively. The final logistic regression models showed no statistically significant differences in the rate of exacerbation both during the entire pregnancy and for each trimester separately between mothers of female and male fetuses after adjusting for all potential confounders listed in the data analysis section (adjusted rate ratio = 1.02; 95% CI: 0.92–1.14 for the entire pregnancy).

## Maternal SABA use by fetal gender

In Table 4, we present the results of the analyses performed to compare the use of SABA between women pregnant with female and male fetuses. The mean doses of SABA used per week in each trimester and during the entire pregnancy were similar in both groups. Moreover, the proportion of women who used at least one dose of SABA per week on average during the entire pregnancy was similar between the groups (62.5% for female and 62.6% for male fetuses). No statistically significant adjusted differences were found between mothers of female and male fetuses as to their use of SABA (adjusted mean difference: 0.004 dose per week; 95% CI: −0.23; 0.24 for the entire pregnancy).

## Maternal ICS use by fetal gender

In Table 5, we present the results of the analysis comparing the mean daily dose of ICS between women pregnant with female and male fetuses. Similar proportions of women used ICS in each trimester and during the entire pregnancy in both groups (41.6% in female and 41.0% in male fetuses during the entire pregnancy). Moreover, the daily doses of ICS were similar between the groups. No statistically significant adjusted differences were found between mothers of female and male fetuses as to their use of ICS (adjusted mean difference: 2.46 μg per day; 95% CI: −4.01; 8.93 for the entire pregnancy).

## Maternal asthma exacerbations in successive pregnancies with a different fetal gender

From the cohort of 11 257 asthmatic pregnant women, we identified 1674 women who had more than one pregnancy during the study period. Among them, 874 had one delivery with a girl and one delivery with a boy during the study period. There was no significant difference in the rate of asthma exacerbations during the entire pregnancy between the male and female fetuses (adjusted rate ratio = 1.07; 95% CI: 0.81–1.42).

# Discussion

In this large cohort study of 11 257 pregnancies of asthmatic women, we detected no significant increase in the rate of maternal asthma exacerbations, the use of ICS and SABA during pregnancy among mothers of female fetuses, whether examined between or within mothers.

Our results are in concord with those of Baibergenova et al. who found no difference in ED visits for asthma between pregnancies of male and female fetuses. This study was based on a large cohort of 109 173 live singleton deliveries reconstructed from a hospital and an ambulatory care administrative database provided by the Canadian Institute for Health Information (CIHI). From this cohort, the investigators first identified all patients who visited an ED during pregnancy and then found that 0.49% and 0.48% of those ED visits were for asthma among women pregnant with a female and a male fetus, respectively ($p$ value >0.05). However, these results should be interpreted with caution since the authors did not take into account the

**Table 2** Asthma related characteristics of study women by fetal gender.

| | In the year before conception | | During pregnancy | |
|---|---|---|---|---|
| | Pregnancies of female fetus ($n = 5529$) | Pregnancies of male fetus ($n = 5729$) | Pregnancies of female fetus ($n = 5529$) | Pregnancies of male fetus ($n = 5729$) |
| ICS use (μg per day),[a] % | | | | |
| 0 | 56.0 | 55.3 | 58.4 | 59.0 |
| 0—500 | 40.3 | 41.3 | 37.6 | 37.6 |
| 500—1000 | 2.6 | 2.4 | 3.0 | 2.2 |
| >1000 | 1.1 | 0.9 | 1.0 | 1.2 |
| SABA use[b] (number of doses per week), % | | | | |
| 0 | 33.4 | 32.9 | 37.5 | 37.5 |
| >0—3 | 34.9 | 34.8 | 32.4 | 32.8 |
| >3 | 31.7 | 32.3 | 30.1 | 29.7 |
| LABA use,[c] % | 2.1 | 1.8 | 1.8 | 1.8 |
| Leukotriene-receptor antagonists use, % | 1.0 | 0.8 | 0.4 | 0.2 |
| Oral corticosteroids use, % | 12.1 | 12.1 | 7.5 | 7.7 |
| ≥1 respiratory physician visit, % | 6.0 | 7.0 | 5.9 | 5.9 |
| ≥1 ED visit for asthma, % | 13.5 | 13.3 | 12.6 | 12.4 |
| ≥1 hospitalization for asthma, % | 1.2 | 1.2 | 1.5 | 1.5 |
| Asthma severity,[d] % | | | | |
| Mild | 81.5 | 82.1 | 82.2 | 82.3 |
| Moderate | 13.4 | 12.6 | 12.7 | 12.3 |
| Severe | 5.1 | 5.3 | 5.1 | 5.4 |
| Asthma control,[d] % | | | | |
| Controlled | 60.6 | 60.1 | 63.2 | 64.0 |
| Uncontrolled | 39.4 | 39.9 | 36.8 | 36.0 |

[a] ICS daily dose in beclomethasone-CFC equivalent over a 12-month period.
[b] SABA: short-acting inhaled $beta_2$-agonist.
[c] LABA: long-acting inhaled $beta_2$-agonist.
[d] Measured with validated database indexes that we developed based on medication use and the need for acute care for asthma.[24]

number of asthmatic women among pregnancies of male and female fetuses.

On the other hand, our results are not in accordance with those of three other smaller studies that found increased markers of uncontrolled asthma among pregnancies of female fetuses,[8—10] but the choice of the outcome and the way it was measured can be put forward to explain the differences between studies. In their blind-controlled prospective study ($n = 34$), Beecroft et al. have found that asthmatic women pregnant with a female fetus reported significantly more shortness of breath (72% vs 31%), nocturnal awakening (55% vs 37%), and general asthma symptoms (50% vs 31%) than women pregnant with a male fetus.[8] However, these self-reported asthma symptoms might not necessarily reflect asthma exacerbations. Moreover, Dodds et al. have evaluated steroids use during pregnancy among a sample of 817 pregnant asthmatic women without having specific data on asthma severity or symptoms and found that it was higher among mothers of a female fetus as opposed to a male fetus (20% vs 14%).[9] This outcome is difficult to interpret since it is unclear whether or not it includes only oral corticosteroids or both inhaled and oral formulations, which in the latter case would not necessarily reflect uncontrolled asthma. Moreover, we cannot conclude on the statistical significance of this difference since no statistical inference was reported in the article. Finally, Kwon et al. used a prospective cohort design to study an objective outcome among 702 pregnant women with asthma, i.e. PEF measures. The PEF was assessed at enrolment and at 21, 29, and 37 weeks of gestation. The 10% reported difference in log diurnal variation of PEF between pregnancies of male and female fetuses reached statistical significance, but we question the clinical significance of the observed difference.[10]

Our study must be interpreted in the light of the following limitations. First, the obtained data from the administrative databases reflect medication dispensing and might not correspond exactly to medication intake. However, there is no reason to believe that the use of the dispensed medications differed between mothers of female and male fetuses. Secondly, the outcome was evaluated for either trimesters or the entire pregnancy and this precluded us to identify short-term changes in asthma control. Thirdly, we did not have access to clinical data, such as the frequency of asthma symptoms and lung

**Table 3** Occurrence of maternal moderate to severe asthma exacerbation in each trimester and during the entire pregnancy, by fetal gender.

| | | *n* total | At least one exacerbation, *n* (%) | Crude OR (F vs M) | Adjusted OR (95% CI) (F vs M) |
|---|---|---|---|---|---|
| 1st trimester | F | 5519 | 378 (6.9) | 1.00 | 1.01 (0.86–1.18)[a] |
| | M | 5721 | 391 (6.8) | | |
| 2nd trimester | F | 5519 | 381 (6.9) | 0.98 | 0.98 (0.84–1.14)[b] |
| | M | 5721 | 408 (7.1) | | |
| 3rd trimester | F | 5474 | 220 (4.0) | 1.02 | 1.03 (0.85–1.24)[c] |
| | M | 5667 | 211 (3.7) | | |
| During pregnancy | F | 5519 | 846 (15.3) | 1.02 | 1.02 (0.92–1.14)[d] |
| | M | 5721 | 861 (15.1) | | |

F: female fetus, M: male fetus.
[a] Adjusted for respiratory specialist visit, asthma severity and asthma control in the year before pregnancy, and ICS use in the first trimester of pregnancy.
[b] Adjusted for socioeconomic status, gestational diabetes, respiratory specialist visit, asthma severity in the year before pregnancy, and ICS use in the second trimester of pregnancy.
[c] Adjusted for gestational diabetes, respiratory specialist visit, asthma severity in the year before pregnancy, and ICS use in the third trimester of pregnancy.
[d] Adjusted for socioeconomic status, respiratory specialist visit during pregnancy, asthma severity and asthma control in the year before pregnancy, and ICS use during pregnancy.

function measures, and this precluded us to evaluate a milder lack of control that could be perceived by the mother.

Our study has also several strengths. One of the biggest strengths is its very large sample size, which provided high power to detect small differences. Indeed, we had 80% power to detect a relative difference of 16% (i.e. RR = 1.16) in the rate of asthma exacerbations between pregnancies of female and male fetus. Moreover, the data obtained from the databases allowed us to identify moderate to severe asthma exacerbations requiring medical attention, which is an outcome that objectively reflects an important aggravation of asthma symptoms. In addition, our cohort included mothers with pregnancies with alternate fetal gender allowing us to compare the outcome between pregnancies of female and male fetuses of the same mother, eliminating inter-patient variability.

In conclusion, we have shown that fetal gender had no significant impact on the rate of maternal moderate to severe asthma exacerbations, use of rescue medications, and ICS during pregnancy. Fetal gender might have a minor impact on maternal asthma symptoms, but this study provides evidence that these changes are not serious enough to lead to a moderate to severe exacerbation. According to our results, it is not recommended to adjust for fetal gender in epidemiologic studies in the field of asthma and pregnancy. Moreover, our results suggest that fetal gender should not be considered to plan

**Table 4** Use of SABA during the entire pregnancy and within each trimester, by fetal gender.

| | | *n* total | At least one dose per week [*n* (%)] | Mean number of doses per week | Crude mean difference (F vs M) | Adjusted mean difference (95% CI) (F vs M) |
|---|---|---|---|---|---|---|
| 1st trimester | F | 5529 | 3083 (55.8) | 4.4 | 0.09 | 0.07 (−0.17 to 0.31)[a] |
| | M | 5728 | 3200 (55.9) | 4.3 | | |
| 2nd trimester | F | 5529 | 3058 (55.3) | 4.6 | 0.03 | −0.003 (−0.27 to 0.26)[b] |
| | M | 5728 | 3172 (55.4) | 4.5 | | |
| 3rd trimester | F | 5484 | 2864 (52.2) | 4.5 | −0.02 | −0.06 (−0.34 to 0.22)[c] |
| | M | 5674 | 2972 (52.4) | 4.5 | | |
| During pregnancy | F | 5529 | 3456 (62.5) | 4.5 | 0.03 | 0.004 (−0.23 to 0.24)[d] |
| | M | 5728 | 3583 (62.6) | 4.4 | | |

F: female fetus, M: male fetus.
[a] Adjusted for socioeconomic status, high risk pregnancy, and respiratory specialist visit during the first trimester of pregnancy, and asthma severity and asthma control in the year before pregnancy.
[b] Adjusted for socioeconomic status and respiratory specialist visit during the second trimester of pregnancy, and asthma severity and asthma control in the year before pregnancy.
[c] Adjusted for socioeconomic status and respiratory specialist visit during the third trimester of pregnancy, and asthma severity and asthma control in the year before pregnancy.
[d] Adjusted for socioeconomic status, high risk pregnancy, pregnancy induced hypertension and respiratory specialist visit during pregnancy, and asthma severity and asthma control in the year before pregnancy.

**Table 5** Use of ICS during the entire pregnancy and within each trimester, by fetal gender.

| | | *n* total | ICS use [*n* (%)] | Mean μg per day | Crude mean difference (F vs M) | Adjusted mean difference (95% CI) (F vs M) |
|---|---|---|---|---|---|---|
| 1st trimester | F | 5529 | 1933 (35.0) | 76.5 | 1.55 | 1.17 (−5.33;7.67)[a] |
| | M | 5728 | 1995 (34.8) | 74.9 | | |
| 2nd trimester | F | 5529 | 1933 (35.0) | 87.1 | 4.36 | 3.63 (−3.82 to 11.09)[b] |
| | M | 5728 | 1974 (34.5) | 82.8 | | |
| 3rd trimester | F | 5484 | 1788 (32.6) | 99.3 | 4.36 | 3.01 (−6.28 to 12.30)[c] |
| | M | 5674 | 1855 (32.7) | 94.9 | | |
| During pregnancy | F | 5529 | 2301 (41.6) | 85.7 | 3.17 | 2.46 (−4.01; 8.93)[d] |
| | M | 5728 | 2348 (41.0) | 82.5 | | |

F: female fetus, M: male fetus.

[a] Adjusted for maternal age at conception, area of residency at delivery, chronic diabetes, chronic hypertension, number of prenatal visits during the first trimester of pregnancy, respiratory specialist visit during the first trimester and asthma severity and asthma control in the year before pregnancy.

[b] Adjusted for maternal age at conception, chronic diabetes, chronic hypertension, number of prenatal visits during the second trimester of pregnancy, respiratory specialist visit during the second trimester and asthma severity in the year before pregnancy.

[c] Adjusted for maternal age at conception, chronic diabetes, chronic hypertension, number of prenatal visits during the third trimester of pregnancy, respiratory specialist visit during the third trimester of pregnancy and asthma severity in the year before pregnancy.

[d] Adjusted for maternal age at conception, area of residency at delivery, gestational diabetes, chronic diabetes, chronic hypertension, number of prenatal visits during pregnancy, respiratory specialist visit during pregnancy and asthma severity and asthma control in the year before pregnancy.

the management of asthma during pregnancy, and that the management should aim at asthma control regardless of the gender of the fetus.

## Competing interests

The authors declare no competing interests for the submitted manuscript.

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